Trop J Nat Prod Res, August 2023; 7(8):3701-3705 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Multicomponent Crystals of Piperine-Nicotinic Acid: The Physicochemical and Dissolution Rate Properties

Maria D. Octavia[1,2], Hasmiwati Hasmiwati[4], Gusti Revilla[5], Erizal Zaini[3]*

[1]*Doctoral Program, Graduate School of Biomedical Sciences, Faculty of Medicine, Andalas University, Padang, 25129, West Sumatera, Indonesia*
[2]*School of Pharmaceutical Science (STIFARM), Padang, 25147, West Sumatra, Indonesia,*
[3]*Department of Pharmaceutics, Faculty of Pharmacy, Andalas University, Padang, 25163, West Sumatera, Indonesia*
[4]*Department of Parasitology, Faculty of Medicine, Andalas University, Padang, 25129, West Sumatra, Indonesia*
[5]*Department of Anatomy, Faculty of Medicine, Andalas University, Padang, 25163, West Sumatra, Indonesia*

ARTICLE INFO

Article history:
Received 05 July 2023
Revised 15 July 2023
Accepted 10 August 2023
Published online 01 September 2023

ABSTRACT

Piperine is included in Class II of the Biopharmaceutical Classification System. Piperine has low solubility in water, resulting in low bioavailability. To improve the physicochemical properties and increase the dissolution rate of piperine, multicomponent crystals were prepared by solvent-drop grinding, using ethanol pa with the addition of nicotinic acid as a coformer. The formation of multicomponent crystals was achieved by varying the mole ratios in the formulas (F): F1 (1:1), F2 (2:1), and F3 (1:2). The multicomponent crystals were characterized by X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), solubility tests, and dissolution profiles using a type II paddle. The XRD patterns showed a decrease in the intensity of the multicomponent crystal formula compared to piperine and the physical mixture. The DSC thermograms showed a decrease in endothermic peaks and enthalpy values. The FTIR spectra confirmed that there was no chemical interaction between piperine and nicotinic acid. SEM analyses showed the formation of new crystal habits. The solubility tests and dissolution profiles showed a significant increase in the amount of solute from the crystalline multicomponent formula compared to intact piperine and the physical mixture. Therefore, the multicomponent piperine-nicotinic acid crystals can improve the physicochemical properties and increase the dissolution rate of piperine.

Keywords: multicomponent crystal, piperine, nicotinic acid, dissolution profile, solvent-drop grinding

Introduction

Piperine belongs to Class II of the Biopharmaceutical Classification System (BCS)[1] as it has low solubility in water,[2] resulting in low bioavailability.[3] Water solubility is an important physicochemical parameter that determines aspects of the formulation and drug delivery in a dosage form.[4] Approximately 40% to up to 70% of active ingredients developed in the pharmaceutical industry have low water solubility.[5,6,7]

Crystal engineering with the formation of multicomponent crystals is one of the techniques used to increase the solubility of piperine.[5,8] Multicomponent crystals can change the physicochemical properties of formulations without changing the chemical properties of the drug and can also increase the rate of dissolution.[9,10] Multicomponent crystals are formed between the molecules of the drug and cocrystal-forming compounds called coformers. Multicomponent crystals are arranged stoichiometrically in the solid state to create new crystal forms through non-covalent bonds, especially through hydrogen bonds formed between the active ingredient and the coformer to attain superior properties for each active form.[10]

*Corresponding author. E mail: erizal.ffua@gmail.com
Tel: +62 813-9502-9297

Citation: Octavia MD, Hasmiwati H, Revilla G, Zaini E. Multicomponent Crystals of Piperin-Nicotinic Acid: The Physicochemical and Dissolution Rate Properties. Trop J Nat Prod Res. 2023; 7(8):3701-3705 http://www.doi.org/10.26538/tjnpr/v7i8.20

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

The coformer must be selected among generally regarded as safe (GRAS) substances so that it is safe to use.[11] Coformers can be excipients or active pharmaceutical ingredients.[12] Coformers can be selected through several approaches based on their functional groups, their tendency to form hydrogen bonds, their formation of supramolecular synthones, or the pKa value between the coformer and the active ingredient.[13,14]

In this study, the coformer was nicotinic acid, which is also known as niacin or vitamin B3, and is a water-soluble vitamin widely used as an additive in foods and cosmetics.[15] Nicotinic acid is often used as a solid pharmaceutical ingredient, which can affect the physicochemical properties of the drug, such as its crystallinity, particle size, particle morphology, and dissolution rate. This ultimately affects the therapeutic effect of the drug.[16,17]

Here, we evaluated the effects of the formation of multicomponent crystals of piperine with nicotinic acid on the physicochemical properties, solubility, and dissolution profiles of the obtained drug.

Materials and Methods

Materials

The materials used in this study were natural piperine (isolated from *Piper nigrum* L. at STIFARM Padang), piperine as references (Sigma Aldrich), nicotinic acid (Sigma Aldrich), acetonitrile HPLC grade (Merck), methanol (Merck), and distilled water (PT. Ikapharmindo Putramas).

Isolation of piperine from Piper nigrum L.

Black pepper simplicia powder was weighed 300 g and then soxhleted using 900 mL methanol until clear. Soxhletation results were filtered and then evaporated with a vacuum evaporator until only 1/3 part

remained. The filtrate formed was added with 20 mL of 10% KOH solution and left for 24 hours. The crystals formed were separated from the solution, and washed with ethyl acetate with the aid of heating. The crystals formed were recrystallized by adding a few drops of hexane. The solution is allowed to form crystals. The crystals formed were separated from the solution, allowed to dry, and stored in a desiccator before use.[1]

Preparation of multicomponent crystals of piperine- nicotinic acid
Multicomponent crystals of piperine and nicotinic acid were prepared by solvent-drop grinding with 1:1, 2:1, and 1:2 mol ratios (piperine: nicotinic acid). Piperine and nicotinic acid were weighed and crushed in a mortar with the addition of ethanol pro analysis. The mixture was crushed for ± 15 mins until a dry and homogeneous mass was formed. The mixture was stored in a desiccator until characterization.[18,19]

Preparation of the piperine-nicotinic acid physical mixture
A physical mixture of piperine and nicotinic acid was prepared with a mole ratio of 2:1 (piperine: nicotinic acid). Piperine and nicotinic acid were weighed and homogenized in a mortar. The mass formed was stored in a desiccator until characterization.[20]

X-ray diffraction (XRD) analysis
An X-ray diffraction (XRD) apparatus (Philips X'Pert Powder PANanalytical, The Netherlands) using a Cu target metal and Kα filter was used. The voltage was 40 Kv. Radiation of 30 mA was spread over the sample's crystal region, as measured by a vertical goniometer. The patterns were obtained using 0.04° step widths with detector resolution at diffraction angles between 10° and 45° at room temperature. The diffraction patterns of piperine, nicotinic acid, their physical mixture, and the multicomponent crystals were obtained.[18,21]

Differential scanning calorimetry analysis (DSC)
Differential scanning calorimetry (DSC) (Setaram DSC 131 Evo, France) analysis was performed. The sample (5 mg) was weighed and heated in an aluminum pan at temperatures of 30–300 °C with a heating rate of approximately 20 °C/min. DSC analyses revealed the melting point patterns of the single compounds, physical mixture, and multicomponent crystals.[22]
Fourier-transform infrared (FT-IR) spectrophotometry
Samples were prepared using the disc method and analyzed with an FT-IR spectrophotometer (Perkin Elmer, USA). The samples were ground into a powder with KBr, then transferred to molds, and compressed into discs under vacuum. The absorption spectrum was recorded at wavenumbers of 400–4000 cm^{-1}. The spectra revealed the functional groups of piperine, nicotinic acid, the physical mixture, and the multicomponent crystals.[1]

Particle surface morphology
Particle surface morphology was determined by scanning electron microscopy (SEM) (Hitachi FLEXSEM 1000, Japan). The powdered sample was placed in a sample holder made of aluminum and coated with gold with a thickness of 10 nm. The samples were then observed at a 1000× magnification. The voltage was set at 20 kV and the current was 12 Ma.[1,21]

Solubility of piperine and multicomponent crystals
The excess amount of intact piperine, the physical mixture, and the multicomponent crystals was put into an Erlenmeyer and 100 mL of distilled water. Then, the Erlenmeyer was shaken (100 rpm) for 24 h at room temperature. After reaching equilibrium, the solution was passed through a Whatman filter paper of 0.45 µm, and was analyzed by high-performance liquid chromatography (HPLC) (Hitachi, Japan). The analysis was performed under optimal conditions to obtain the peak area so that the concentration of dissolved piperine in the aqueous medium could be calculated.[20,21]

In vitro dissolution rate profile
Dissolution rate profile were carried out using apparatus II (paddle type) (Copley Scientific NE4-COPD, UK). The medium used was distilled water, to which 900 mL of 0.1% sodium lauryl sulfate was added. The temperature was set at 37 ± 0.5°C with a stirring speed of 50 rpm. Once this temperature was reached, a sample containing the equivalent of 50 mg of piperine was poured into the dissolution vessel. A volume of 5 mL of solution was taken at 5, 10, 15, 30, 45, and 60 mins. When pipetting, the solution that had been taken was replaced with the same volume of water at the same temperature. The solution was passed through a 0.45 µm Whatman filter paper and analyzed using HPLC (Hitachi, Japan) to obtain the peak area and calculate the percentage of dissolved substance. The results of the calculations were used to build a dissolution profile curve (i.e., a curve showing the relationship between time and the percent dissolution of piperine).[18,22,23]

Results and Discussion

Solid State Characteristics of multicomponent crystals and the physical mixture
XRD
XRD analysis provides information about the crystal structure and degree of crystallinity of an active pharmaceutical ingredients in the solid state.[24] The results of the XRD analysis are presented in Figure 1. The piperine diffractogram shows a very sharp diffraction pattern at 2θ angles of 12.93º, 14.75º, and 19.27º with intensities of 32720.46, 88185, and 72246.1, respectively.[1] The diffractogram pattern of nicotinic acid shows a very sharp diffraction pattern at 2θ angles of 15.5626º, 20.4376º, 21.3216º, 24.8966º, 26.0536º, 26.9766º, and 28.0686º, with intensities of 4321.42, 2242.124, 1374.58, 3131.432, 3833.336, 4757,394, and 2989.86, respectively. This indicates that piperine and nicotinic acid are in crystal form.[23]
In the diffractogram of the physical mixture and multicomponent crystals (piperine-nicotinic acid), there was a notable decrease in the intensity of the piperine and nicotinic acid interference peaks, which indicate a decreases in the crystallinity of the multicomponent crystal, but there is no formation of the new crystal structure. This decrease in intensity occurred because of a reduction in the particle size of piperine by solvent-drop grinding.[25]

DSC
Thermal analysis using DSC is useful for detecting changes in the thermodynamic properties of samples exposed to heat. With DSC, thermal events can be detected in the form of glass transitions, crystallization, melting and degradation, and melting energy.[26,27,28] In multicomponent formation, DSC can be used for selecting suitable coformers to produce cocrystals with the desired molecule, to detect polymorphic transformations of the drug or coformer, and to detect the formation of new phases such as cocrystals.[24]

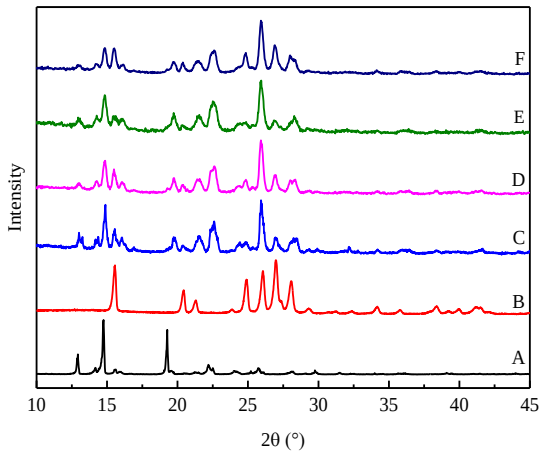

Figure 1: Diffractogram of (A) piperine, (B) nicotinic acid, (C) the physical mixture (piperine-nicotinic acid (2:1)), and multicomponent crystals (piperine-nicotinic acid): (D) F1 (1:1), (E) F2 (2:1), and (F) F3 (1:2).

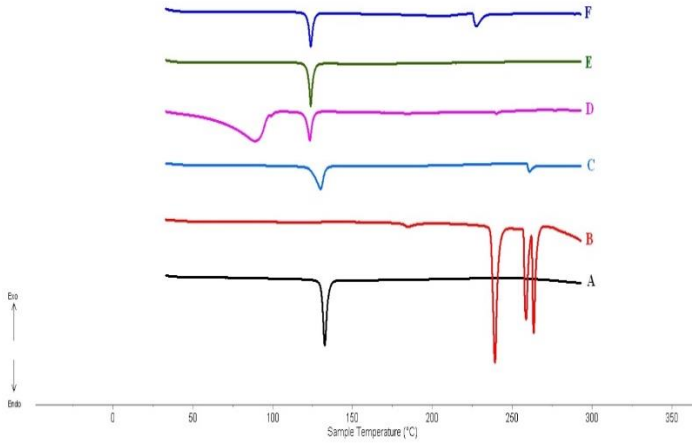

Figure 2: Thermograms of (A) piperine, (B) nicotinic acid, (C) the physical mixture (piperine-nicotinic acid (2:1)), and multicomponent crystals (piperine-nicotinic acid): (D) F1 (1:1), (E) F2 (2:1), and (F) F3 (1:2).

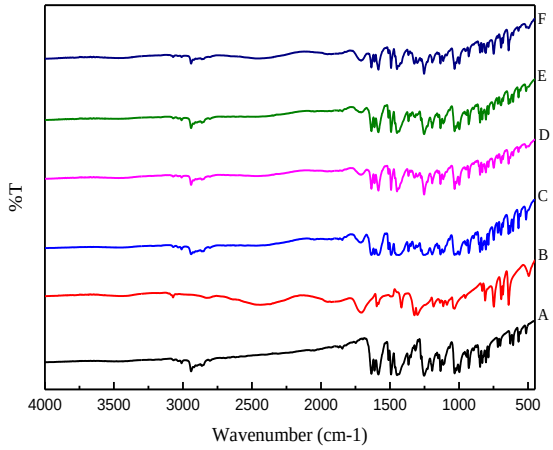

Figure 3: FT-IR spectra of (A) piperine, (B) nicotinic acid, (C) physical mixture (piperine-nicotinic acid (2:1)), and multicomponent crystals (piperine-nicotinic acid): (D) F1 (1:1), (E) F2 (2:1), and (F) F3 (1:2).

The results of the DSC analyses are presented in Figure 2. The DSC thermograms show an endothermic peak, which indicates that thermal energy is required to melt the samples. On the piperine thermogram, there is a distinctive and sharp endothermic peak with a melting point of 132.579ºC and an enthalpy of 106.481 J/g.[1] The nicotinic acid thermogram displays an endothermic peak with a melting point of 238.827 ºC and an enthalpy of 155.508 J/g.[23] This indicates that piperine and nicotinic acid are in the form of crystals that require a large amount of energy to melt.[24]

In the thermogram of the physical mixture of piperine and nicotinic acid, two peaks appeared, corresponding to the endothermic peaks of piperine and nicotinic acid, with a shift in melting point and a decrease in enthalpy. If a binary mixture with a certain heating rate produces two endothermic peaks corresponding to the melting point of each component, the binary mixture is a physical mixture where there is no intermolecular interaction.[24] In the multicomponent crystal (piperine-nicotinic acid), the decrease in the melting point and enthalpy of piperine indicates an interaction between piperine and nicotinic acid. The low melting point occurs because the lattice energy decreases, increasing the solubility of piperine. In addition, the lowering of the melting point also indicates that the solid is a eutectic mixture, which is characterized by a single endothermic peak corresponding to the mixture of the drug and coformer. This finding was supported by the XRD results.[29]

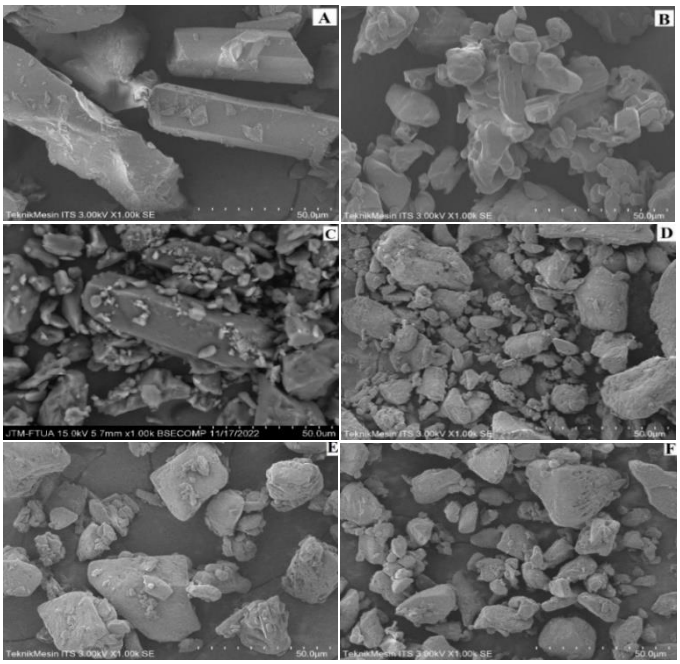

Figure 4: Micrographs of (A) piperine, (B) nicotinic acid, (C) the physical mixture (piperine-nicotinic acid (2:1)), and multicomponent crystals (piperine-nicotinic acid): (D) F1 (1:1), (E) F2 (2:1), and (F) F3 (1:2) at a 1000× magnification.

FT-IR Spectroscopy

FT-IR spectrophotometry is a technique used to characterize and identify hydrogen bonds and molecular conformations in multicomponent crystals.[30] The FTIR spectra show typical peaks at specific wavenumbers that correspond to the molecular structure of piperine and nicotinic acid. The FT-IR spectrum of piperine shows typical transmittance peaks at the aromatic CH functional group at wavenumber 2941 cm^{-1}, aliphatic CH in the methylenedioxy group at wavenumber 2864 cm^{-1}, C=O at wavenumber 1635 cm^{-1}, aromatic C=C at wavenumber 1449 cm^{-1}, and asymmetric =C-O-C at wavenumber 1235 cm^{-1} in the piperine structure.[1,31] The FT-IR spectrum of nicotinic acid produced transmittance peaks, namely those corresponding to the functional group CH at wavenumbers 3070 cm^{-1} and 2840 cm^{-1}, C=C at wavenumber 1596 cm^{-1}, C=N at wavenumber 1417 cm^{-1}, asymmetric COO^- at wavenumber 1710 cm^{-1}, C=O at wavenumber 1323 cm^{-1}, C-N at wavenumber 1302 cm^{-1}, and C-OH at wavenumber 1185 cm^{-1}.[23,32]

The FTIR spectra of the physical mixture and multicomponent crystals of piperine and nicotinic acid exhibited the characteristic transmittance peaks of piperine and nicotinic acid, thus confirming the presence of both compounds in the formula. The FTIR spectra of the physical mixture and the multicomponent crystals confirm that each compound maintains its structural identity and that there is no chemical interaction between piperine and nicotinic acid. The result of the FTIR spectra analysis are presented in Figure 3 and Table 1.

Particle surface morphology

The SEM micrographs revealing the particle surface morphology of the samples with a magnification of 1000× are presented in Figure 4. The morphology of piperine exhibits the shape of a crystal rod with an irregular surface. The surface morphology of nicotinic acid particles shows an aggregate shape with an irregular surface.[23] The surface morphology of the physical mixture shows the presence of nicotinic acid particles on the surface of the piperine particles. The surface morphology of the multicomponent crystals (F1, F2, and F3) shows an irregular shape with an uneven surface and a decrease in the size distribution of the powder particles.

Table 1: Functional groups of piperine, nicotinic acid, the physical mixture (piperine-nicotinic acid (2:1)), and multicomponent crystals (piperine-nicotinic acid): F1 (1:1), F2 (2:1), and F3 (1:2).

Functional groups	Wavenumber (cm^{-1})					
	Piperine	Nicotinic acid	Physical mixture	F1 (1:1)	F2 (2:1)	F3 (1:2)
Aromatic CH	2941		2942	2941	2941	2941
Aliphatic CH	2863		2864	2863	2864	2864
C=O	1634		1636	1634	1635	1634
Aromatic C=C	1449		1449	1449	1449	1449
=C-O-C	1253		1254	1253	1254	1253
C-H		3070	3011	3010	3011	3072
COO^-		1708	1714	1711	1723	1711
C=C		1596	1587	1584	1584	1584
C=N		1417	1434	1435	1434	1419
C=O		1323	1323	1324	1324	1324
C-N		1301	1306	1303	1305	1303
C-OH		1186	1194	1194	1194	1194

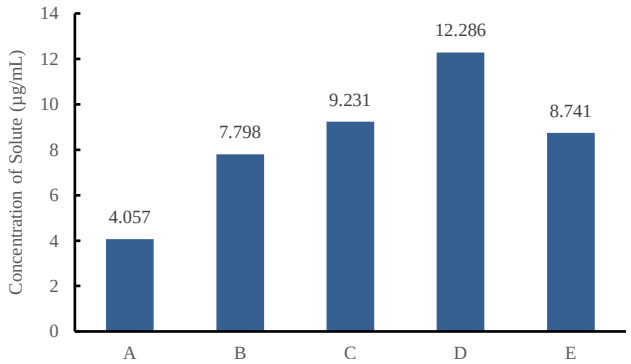

Figure 5: Solubility of (A) piperine, (B) the physical mixture (piperine-nicotinic acid (2:1)), and multicomponent crystals (piperine-nicotinic acid): (C) F1 (1:1), (D) F2 (2:1), and (E) F3 (1:2).

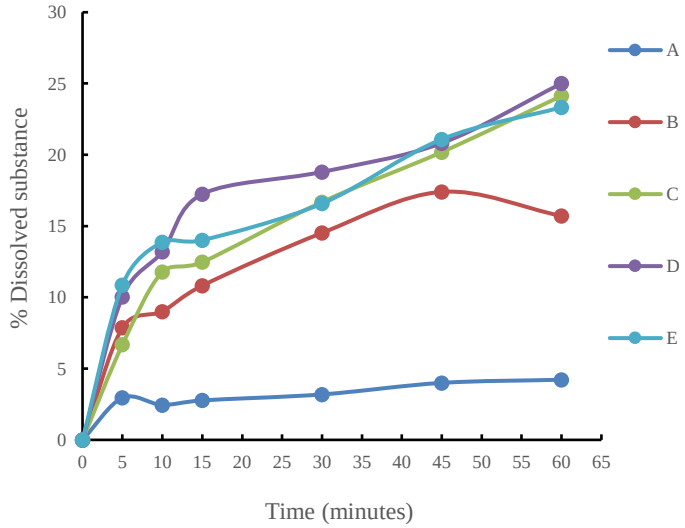

Figure 6: Dissolution curves of (A) piperine, (B) the physical mixture (piperine-nicotinic acid (2:1)), and multicomponent crystals (piperine-nicotinic acid): (C) F1 (1:1), (D) F2 (2:1), and (E) F3 (1:2).

Solubility tests of piperine, the physical mixture, and multicomponent crystals

The solubility tests showed a significant increase in the solubility of the multicomponent crystal formula compared to the physical mixture. The concentration of solute (piperine) was 4.057 ± 0.013 in the dissolved piperine, 7.798 ± 0.028 in the physical mixture, 9.231 ± 0.072 in the F1 multicomponent crystal, 12.286 ± 0.241 in F2, and 8.741 ± 0.156 in F3. Compared to intact piperine, the F2 multicomponent crystal showed the highest solubility increase (3.028 times) compared to F1 (2.275 times), F3 (2.154 times), and the physical mixture (1.922 times). Figure 5 shows the results of the solubility tests.

In vitro dissolution rate profile

The dissolution test was carried out using apparatus II (paddle type) with a stirring speed of 50 rpm. The medium used was water containing 900 mL of 0.1% sodium lauryl sulfate at a temperature of 37 ± 0.5 °C. The results of the piperine dissolution test of the physical mixture and multicomponent crystals are displayed in Figure 6. At 60 mins, 4.222 ± 0.205 of piperine, 15.709 ± 0.573 of the physical mixture, 24.129 ± 0.096 of the F1 multicomponent crystal, 25.000 ± 0.124 of F2, and 23.328 ± 0.670 of F3 dissolved. The dissolution results showed that there was a significant increase in the percentage of dissolved substance from the multicomponent crystals compared to piperine and the physical mixture. F2 showed the highest dissolution profile with an increase of 5.924 times, followed by F1 (5.718 times), F3 (5.528 times), and the physical mixture (3.723 times) compared to piperine. The local solubilization effect induced by nicotinic acid in the diffusion layer around the piperine particles was responsible for the notable increase in the dissolution rate of piperine from the multicomponent crystals. This phenomenon increase piperine solubility in the dissolving medium, resulting in quicker dissolution rate. Furthermore, the rise in dissolution rate might be related to changes in the eutectic mixture's thermodynamic characteristics, such as high free energy, greater molecular mobility and weaker intermolecular interaction.[28,29]

Conclusion

Based on the physicochemical characteristics revealed by XRD, DSC, FT-IR, and SEM analyses, we can conclude that the piperine formulation with nicotinic acid as a coformer generates multicomponent crystals by solvent-drop grinding. The solubility tests revealed a significant increase in the concentration of dissolved piperine from multicomponent crystal formulas compared to intact piperine and the physical mixture. The dissolution profile showed increased percent dissolution of the crystalline multicomponent formula compared to piperine. Therefore, the preparation of multicomponent crystals of

piperine-nicotinic acid can improve the physicochemical properties and increase the dissolution rate of piperine

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors would like to thank the Directorate of Research and Community Service - National Research and Innovation Agency (DRPM-Kemenristek/BRIN) of the Republic of Indonesia for their financial assistance (grant number: 012/E5/PG.02.00.PL/2023.

References

1. Zaini E, Riska D, Oktavia MD, Ismed F, Fitriani L. Improving dissolution rate of piperine by multicomponent crystal formation with saccharin. Res J Pharm Tech. 2020; 13(4):1926–1930.
2. Vasavirama K, Upender M. Piperine: A valuable alkaloid from piper species. Int J Pharm Pharm Sci. 2014; 6(4):34–38.
3. Pachauri M, Gupta ED, Ghosh PC. Piperine loaded PEG-PLGA nanoparticles: Preparation, characterization and targeted delivery for adjuvant breast cancer chemotherapy. J Drug Del Sci Tech. 2015; 29:269–282.
4. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000; 44(1):235–249.
5. Savjani KT, Gajjar AK, Savjani JK. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm. 2012; 2012:1–10.
6. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci (2006); 29:278–287.
7. Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan. Mol Pharm. 2006; 3(6):631–643.
8. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, Porter, CJH. Strategies to address low drug solubility in discovery and development. Pharmacol Rev. 2013; 65(1):315–499.
9. Grothe E, Meekes H, Vlieg E, Ter Horst JH, De Gelder R. Solvates, Salts, and Cocrystals: A Proposal for a Feasible Classification System. Crys Growth Des. 2016; 16(6):3237–3243.
10. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. J Pharm Sci. 2006; 95(3):499–516.
11. Steed JW. The role of co-crystals in pharmaceutical design. Trends Pharmacol Sci. 2013; 34(3):185–193.
12. Sekhon B. Pharmaceutical co-crystals - a review. Ars Pharm. 2009; 50(3):99–117.
13. Aitipamula S, Banerjee R, Bansal AK, Biradha K, Cheney ML, Choudhury AR, Desiraju GR, Dikundwar AG, Dubey R, Duggirala N, Ghogale PP, Ghosh S, Goswami PK, Goud NR, Jetti RRKR, Karpinski P, Kaushik P, Kumar D, Kumar V, Zaworotko MJ. Polymorphs, Salts, and Cocrystals: What's in a Name?. Crys Growth Des. 2012; 12(5):2147–2152.
14. Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ. Pharmaceutical cocrystals: Along the path to improved medicines. Chem Comm. 2016; 52(4):640–655.
15. Carlson LA. Nicotinic acid: The broad-spectrum lipid drug. A 50th anniversary review. J Intern Med. 2005; 258(2):94–114.
16. Brittain HG. Polymorphism in pharmaceutical solids. (2nd Ed). New York: M. Dekker: 1999.
17. Gonçalves EM, Bernardes CES, Diogo HP, Minas Da Piedade ME. Energetics and structure of nicotinic acid (Niacin). J Physic Chem B. 2010; 114(16):5475–5485.
18. Zaini E, Afriyani, Fitriani L, Ismed F, Horikawa A, Uekusa H. Improved solubility and dissolution rates in novel multicomponent crystals of piperine with succinic acid. Sci Pharm. 2020; 88(2):1-12.
19. Jessica A, Naura R, Hasanah U, Zaini E, Fitriani L. Pembentukan Multikomponen Kristal Piperin Dan Kuersetin. J Pharm Sci. 2021; 4(2):1–11.
20. Yuliandra Y, Zaini E, Syofyan S, Pratiwi W, Putri L N, Pratiwi YS, Arifin H. Cocrystal of ibuprofen–nicotinamide: Solid-state characterization and in vivo analgesic activity evaluation. Sci Pharm. 2018; 86(2):1-11.
21. Octavia MD, Halim A, Zaini E. Preparation of Simvastatin-β-Cyclodextrin inclusion complexes using coevaporation technique. J Chem Pharm Res. 2015; 7(2):740–747.
22. Zaini E, Fitriani L, Sari RY, Rosaini H, Horikawa A, Uekusa H. Multicomponent Crystal of Mefenamic Acid and N-Methyl-D-Glucamine: Crystal Structures and Dissolution Study. J Pharm Sci. 2019; 108(7):2341–2348.
23. Sari YN, Zaini E, Ismed F. Peningkatan laju disolusi piperine dengan pembentukan multikomponen kristal menggunakan asam nikotinat. J Sains Farm Klin. 2019 6(2):180-185.
24. Sathisaran I, Dalvi SV. Engineering cocrystals of poorlywater-soluble drugs to enhance dissolution in aqueous medium. Pharmaceutics. 2018; 10(3):58-74.
25. Zaini E, Sumirtapura YC, Halim A, Fitriani L, Soewandhi SN. Formation and characterization of sulfamethoxazole-trimethoprim cocrystal by milling process. J Appl Pharm Sci. 2017; 7(12):169–173.
26. Fitriani L, Afriyanti I, Afriyani, Ismed F, Zaini E. Solid dispersion of usnic acid–HPMC 2910 prepared by spray drying and freeze drying techniques. Orient J Chem. 2018; 34(4):2083–2088.
27. Bhusnure O, Kazi P, Gholve S. Solid Dispersion: an Ever Green Method for Solubility Enhancement of Poorly Water Soluble Drugs. Int J Res in Pharm Chem. 2014; 4(4):906–918.
28. Berry DJ, Steed JW. Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design. Adv Drug Del Rev. 2017; 117:3–24.
29. Cherukuvada S, Row TNG. Comprehending the Formation of Eutectics and Cocrystals in Terms of Design and Their Structural Interrelationships. Crys Growth Des. 2014; 14:4187−4198.
30. Chi Z, Wang M, Yang L, Li X, Cong X, Liu S, Cai B. Fourier Transform Near-Infrared Spectroscopy Used for Purity Determination of Rhein-L-arginine Cocrystal (Argirein). Anal Sci, 2013; 29(6):661–664.
31. Ren T, Hu M, Cheng Y, Shek TL, Xiao M, Ho NJ, Zhang C, Leung SSY, Zuo Z. Piperine-loaded nanoparticles with enhanced dissolution and oral bioavailability for epilepsy control. Eur J Pharm Sci. 2019; 137:1-8.
32. Trivedi MK, Branton A, Trivedi D, Nayak G, Bairwa K, Jana S, Trivedi MK, Branton A, Trivedi D, Nayak G, Bairwa K. Spectroscopic Characterization of Disulfiram and Nicotinic Acid after Biofield Treatment. J Anal Bioanal Tech. 2016; 6(5):1–5.